In Vitro Adsorption of Various Pharmaceuticals to Montmorillonite

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Abstract □ Dissolution and dialysis studies showed that cationic drugs and certain nonionic drugs bind strongly to montmorillonite clay. The quantity of drug bound by one unit of clay varied considerably. Anionic drugs were weakly bound, and less bioavailability problems would be anticipated with these medicinals. The mechanism of binding of cationic drugs to montmorillonite was proposed as a two-step process: a cation-exchange reaction followed by strong surface chemisorption.

Keyphrases □ Montmorillonite—*in vitro* adsorption by various pharmaceuticals, dissolution and dialysis studies, mechanism of binding □ Adsorption—various pharmaceuticals to montmorillonite *in vitro*, dissolution and dialysis studies, mechanism of binding □ Clay adsorbents—montmorillonite, *in vitro* adsorption by various pharmaceuticals, dissolution and dialysis studies, mechanism of binding

Montmorillonite, a complex colloidal magnesium aluminum silicate clay, is widely used in cosmetics and pharmaceuticals. It is available in several grades for special applications, a factor that has increased its potential in formulation. The general properties of montmorillonite were reviewed previously (1).

Various grades of montmorillonite were studied for use as disintegrants, binders, and lubricants (2). Another study (3) found that the procedure used to incorporate montmorillonite as the disintegrating agent affects the disintegration time of compressed tablets. Other reports concern the use of montmorillonite as a disintegrating (4–6) and granulating (7) agent. Recently, the influence of electrolytes on the desorption of neomycin from attapulgite and montmorillonite clays was investigated (8).

For many organic compounds, the mechanism of interaction with unneutralized montmorillonite was ion exchange (9). This mechanism also was suggested (10) for the inactivation of cationic antiseptics by a suspension of another montmorillonite clay, bentonite.

Surface adsorption was suggested as the mechanism in the interaction between montmorillonite and benzoic acid (11). This report discussed whether solutes are adsorbed on the surface or in the interlaminar space of neutralized montmorillonite as proposed earlier (12).

Although the literature contains numerous examples of montmorillonite performing different functions in pharmaceutical dosage forms, few reports concern the availability or dissolution of the drug from such dosage forms. The purposes of these studies were to determine the types of drugs that bind to montmorillonite, to investigate the extent of binding *via* dissolution–dialysis studies, and to shed light on the complex nature of binding between drugs and montmorillonite clay.

EXPERIMENTAL

Materials—The following were used: amphetamine sulfate[1], chlorpheniramine maleate[2], propoxyphene hydrochloride[3], caffeine[4], anhydrous theophylline NF, sodium salicylate NF, sulfanilamide NF, and montmorillonite[5]. The cellulose membrane[6] had an average pore diameter of 50 Å, an average dry thickness of 0.001 cm (0.00055 in.), and an average rewet thickness of 0.003 cm (0.00128 in.).

Preparation of Drug–Montmorillonite Sample—Montmorillonite flakes were ground and passed through a No. 60 sieve. The desired quantity of clay was weighed and added to sufficient deionized water, warmed to 80°, to make a 1% (w/v) suspension. Then the mixture was stirred with a magnetic stirrer and allowed to hydrate for 12 hr at room temperature.

A dilute solution of the drug was added slowly while the mixture was stirred vigorously. After drying under vacuum at temperatures below 35°, the sample was weighed, ground, passed through a No. 60 sieve, and then rotated end-over-end in a capped bottle for 2 hr to ensure uniformity. Such complexes with the different drugs were prepared by varying the amount of montmorillonite.

Unless otherwise stated, montmorillonite regular was the grade of clay used. Some studies utilized montmorillonite neutral, while others employed nonaqueous solvents for the equilibrating medium.

To assess the influence of electrolytes on the binding of drugs to regular montmorillonite, clay suspensions were prepared in 500-ml volumetric flasks. The magma was prepared as previously described, using 2 g of montmorillonite and 200 ml of warm deionized water. The 500 mg of drug was added either before or after the addition of the electrolyte. Each step in this process was allowed to stand and equilibrate for 12 hr at room temperature before the next component was added.

The pharmaceutical complexes discussed in this report are written as x:y, where x represents the quantity of drug and y represents the quantity of montmorillonite. For example, 1:10 represents 1 g of drug/10 g of clay.

The diffuse reflectance spectroscopy investigation employed 1:10 drug–montmorillonite adsorbates, prepared as the equilibrated sample and the physical mix. Chlorpheniramine maleate was the drug studied. Water was used as the solvent for equilibration, and the physically mixed sample was prepared by light trituration of the drug and clay. The montmorillonite used for the reference and the physical mix was hydrated and dried so it would be in the same physical state as the equilibrated sample. All powders were passed through a No. 100-mesh screen.

Apparatus for Dissolution–Dialysis Studies—The Lach dissolution–dialysis cell utilized for these studies consisted of two plexiglass compartments. The dissolution compartment (A) was separated from the dialysate (B) by a cellophane membrane. This apparatus was described previously and utilized in an earlier study (13). In all studies, 600 ml of medium was used in Compartment A and 350 ml was in the flask attached to Compartment B. The sample size varied for each drug as the ratio of drug to montmorillonite was changed.

The equilibrated sample was accurately weighed and added to the dissolution medium *via* the orifice in Compartment A. No problems were encountered in the wetting of the samples. However, some pure drugs did not wet readily; when aggregates formed at the surface, they were lightly broken up with a microspatula within seconds of adding the drug to the medium. Aliquots of 3 ml were withdrawn from Compartment A at periodic intervals by a pipet adapted with a sintered-glass filter of medium porosity.

Similarly, samples were extracted from the dialysate flask. These aliquots were appropriately diluted, and absorbance measurements were determined at the required wavelengths[7]. To maintain a constant

[1] J. H. Walker & Co., Mount Vernon, N.Y.

[2] Schering Corp., Union, N.J.
[3] Eli Lilly & Co., Indianapolis, Ind.
[4] Eastman-Kodak, Rochester, N.Y.
[5] Veegum, regular and neutral grades, R. T. Vanderbilt Co., New York, N.Y.
[6] Neflex dialysis membrane, Union Carbide Corp., New York, N.Y.
[7] Gilford model 240 spectrophotometer.

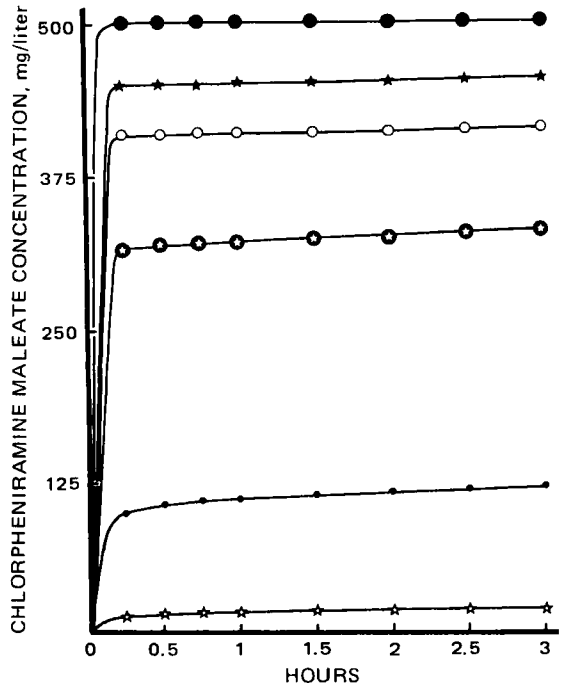

Figure 1—*Dissolution profiles of chlorpheniramine maleate–montmorillonite samples in different drug–excipient ratios in 0.1 N HCl at 25°. Key: ●, drug alone; ★, 1:0.5; ○, 1:1; ◎, 1:2; •, 1:5; and ☆, 1:10 and 1:20.*

volume in both compartments after the removal of samples from A and B, the same volume of fresh dissolution and dialysate medium was replaced. Accumulation corrections were made for removed samples.

RESULTS AND DISCUSSION

Dissolution data obtained with the dissolution–dialysis cell for various drug–montmorillonite complexes indicated the quantity of drug released from the complex. In some instances, however, a better index of true availability of a drug may be determined *via* dialysis studies. Not only the drug but also the drug–excipient complex is often estimated when working with macromolecules, giving erroneous results for dissolution determinations. This problem exists if the excipient is a high molecular weight, water-soluble material. Such a complex could pass through the filtering device used for sampling and thereby indicate an increase in dissolution rate over that of the pure drug.

The three cationic drugs chosen for investigation were chlorpheniramine maleate, amphetamine sulfate, and propoxyphene hydrochloride.

Chlorpheniramine Maleate–Montmorillonite—The dissolution data for the drug–montmorillonite samples, containing 300 mg of chlorpheniramine maleate with varying amounts of clay, in 0.1 *N* HCl are presented in Fig. 1. The initial increase in the amount of drug in solution represented the quantity of drug uncomplexed with the clay. The plateau effect suggested that the drug was strongly bound to the montmorillonite and that desorption was very slow in an acid medium. Particles of the complex appeared not to rehydrate in acid solution, as evidenced by the slight cloudiness of the dissolution medium, by the minimal increase in the viscosity of the medium, and by the gritty texture of the undissolved particles at the conclusion of each experiment.

The dialysis plots in Fig. 2 showed that drug release from the complex followed the same order as in the family of curves for the dissolution profiles. After 3 hr, 20% of the pure drug had dialyzed into Compartment B when no clay was present in the sample.

It can be assumed that the total quantity of antihistamine released after 15 min was due to uncomplexed or free drug. A plot of the concentration of chlorpheniramine maleate in solution after 15 min *versus* the percent of montmorillonite in the various solid complexes appears in Fig. 3. By extrapolating the curve to the *x*-axis, it was possible to determine the quantity of montmorillonite required to complex a

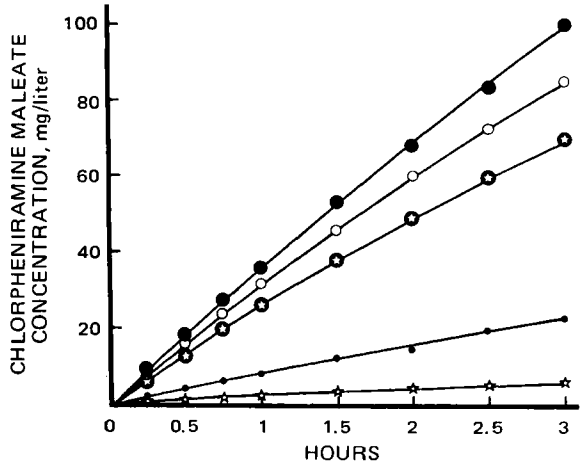

Figure 2—*Dialysis profiles of chlorpheniramine maleate–montmorillonite samples in different drug–excipient ratios in 0.1 N HCl at 25°. Key: ●, drug alone; ○, 1:1; ◎, 1:2; •, 1:5; and ☆, 1:10 and 1:20.*

certain amount of drug. According to this plot, a chlorpheniramine maleate–montmorillonite sample must contain 87% montmorillonite to complex all of the drug, *i.e.*, a ratio of 13:87 or 1:6.7. Therefore, 6.7 g of montmorillonite removes 1 g of drug from solution. If higher ratios are present, *i.e.*, greater than 6.7 g of clay/g of drug, no free drug would be available and only drug released from the complex would be detected. A more extensive treatment of the data derived from such a plot will be discussed with the propoxyphene hydrochloride–montmorillonite system.

Amphetamine Sulfate–Montmorillonite—All samples investigated contained 800 mg of amphetamine sulfate. The dissolution profiles (Fig. 4) showed that this drug was less tightly bound to montmorillonite than chlorpheniramine maleate. When the dissolution curves were compared for both drugs (Figs. 1 and 4) present as the 1:5 complex, the slight increase in the slope of the profile for the amphetamine complex represented an increase of 5% of drug concentration in the acid medium after 3 hr. As for chlorpheniramine maleate, the dialysis data for each complex were clearly separated and occurred in the same rank order as the family of curves for the dissolution plots.

Figure 4 also shows a marked difference in the amount of drug released from the 1:10 and 1:20 complexes, indicating that a higher ratio

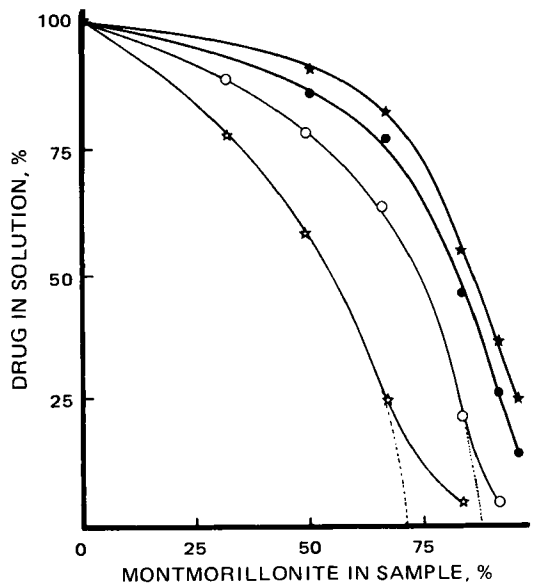

Figure 3—*Influence of the percent montmorillonite in the drug–clay adsorbate on the amount of drug in solution after a certain time period. Key: ☆, propoxyphene hydrochloride after 15 min; ○, chlorpheniramine maleate after 15 min; ●, amphetamine sulfate after 15 min; and ★, amphetamine sulfate after 30 min.*

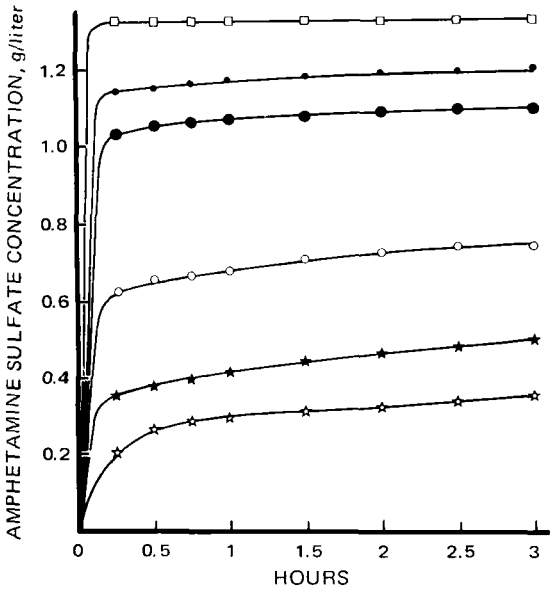

Figure 4—*Dissolution profiles of amphetamine sulfate–montmorillonite samples in different drug–excipient ratios in 0.1 N HCl at 25°. Key:* □, *drug alone;* •, *1:1;* ●, *1:2;* ○, *1:5;* ★, *1:10; and* ☆, *1:20.*

than 1:20 might be required to complex all of the drug. A plot of the amount of amphetamine sulfate in solution as a function of the percent of montmorillonite in the solid sample is shown in Fig. 3. The separation between the curves represents the quantity of drug released from the sample from 15 min to 3 hr for a particular ratio of drug and excipient.

However, extrapolation of these plots indicates that more than 100% montmorillonite would be required in a drug–montmorillonite complex to remove all drug from solution. One possible explanation is that a desorption process is taking place in the first 15 min. Thus, when the drug is desorbed from the complex in an acid medium, only a limited amount of data can be obtained using this method; the maximum adsorptive capacity of the clay cannot be derived from these profiles.

Propoxyphene Hydrochloride–Montmorillonite—The dissolution profiles for the montmorillonite complexes of this drug are illustrated in Fig. 5. All samples contained 800 mg of propoxyphene

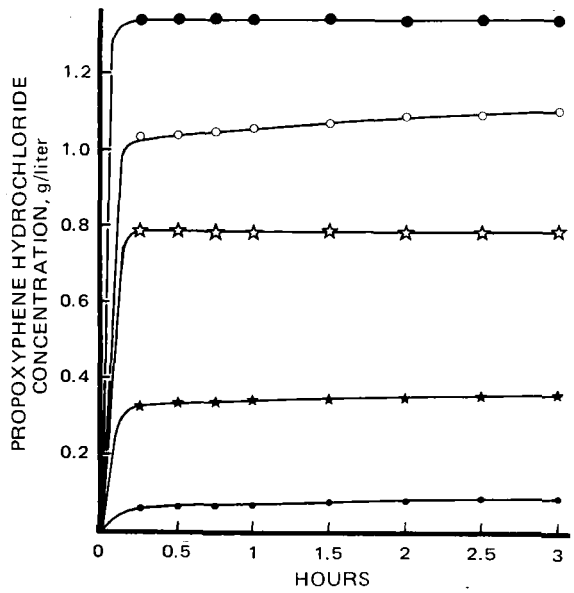

Figure 5—*Dissolution profiles of propoxyphene hydrochloride–montmorillonite samples in different drug–excipient ratios in 0.1 N HCl at 25°. Key:* ●, *drug alone;* ○, *1:0.5;* ☆, *1:1;* ★, *1:2; and* •, *1:5.*

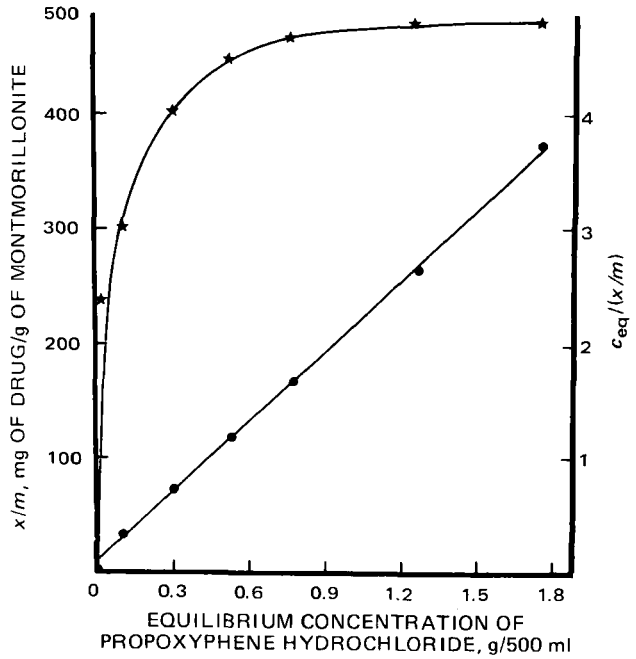

Figure 6—*Adsorption isotherm for propoxyphene hydrochloride by montmorillonite. Key:* ★, x/m versus *equilibrium concentration; and* ●, c_{eq}/(x/m) versus *equilibrium concentration.*

hydrochloride with varying amounts of montmorillonite clay. The dissolution data indicated that propoxyphene was very strongly bound, and the presence of the plateau in the dissolution profiles demonstrated that little drug was released in the acid solution. The dialysis data for the various drug–clay complexes appeared in the same rank order as the dissolution profiles.

Figure 6 shows the data plotted according to the Langmuir equation (14), which may be written as:

$$\frac{c}{x/m} = \frac{1}{ab} + \frac{c}{b} \qquad \text{(Eq. 1)}$$

where c is the equilibrium concentration of solute, x/m is the mass of solute (x) per gram (m) of the adsorbate, b is the constant called the "adsorptive capacity," and a is the constant called the "adsorption coefficient." The linear adsorption isotherm denoted monomolecular adsorption of drug to the clay. If deviations from linearity in the plot of $c/(x/m)$ *versus* c had occurred, the presence of a weak, electrostatically bound second layer of drug molecules would have been indicated. This effect was not observed; propoxyphene appeared to be monomolecularly adsorbed.

In addition, the b value or maximum adsorptive capacity of montmorillonite for this drug may be calculated. By extrapolating the plateau region of the curve in Fig. 6 back to the y-axis, the intercept gives the value for b equal to 480. The value of b can also be calculated from the linear plot and is equal to the reciprocal of the slope (b = 490). Therefore, the maximum amount of propoxyphene hydrochloride that 1 g of montmorillonite can adsorb is approximately 485 mg (approximately a 1:2.1 ratio).

The amount of propoxyphene hydrochloride in solution after 15 min, as a function of montmorillonite concentration, appears in Fig. 3. By extrapolating the curve to the x-axis, it can be shown that the sample must contain 71% clay to remove all drug from solution. Therefore, 1 g of drug was removed from solution by 2.3 g of clay. Thus, by utilizing dissolution data collected after 15 min for the various drug–excipient ratios in the acid medium, the maximum adsorptive capacity of the clay for propoxyphene was calculated to be 410 mg/g of montmorillonite.

The discrepancy between these two experimentally determined b values (410 *versus* 485) could partly be due to the slight amount of desorption of drug from the clay during the first 15 min. However, the higher value of b was determined from equilibrated liquid mixtures of hydrated clay and drug. The lower b value was determined from solid dehydrated particles of drug–montmorillonite complex in the acid medium. It is possible that during the slow dehydrating process, as water is removed, there is a slight but continuous change in the

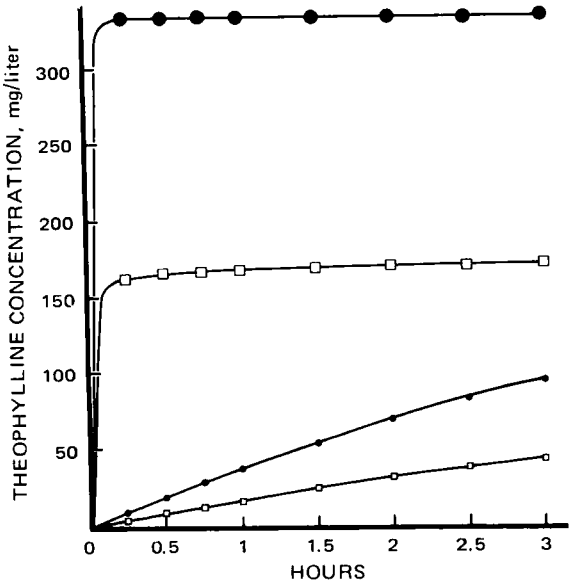

Figure 7—*Dissolution and dialysis profiles of theophylline–montmorillonite samples in different drug–excipient ratios in 0.1 N HCl at 25°. Key: ●, dissolution, drug alone; □, dissolution, 1:5; •, dialysis, drug alone; and ▫, dialysis, 1:5.*

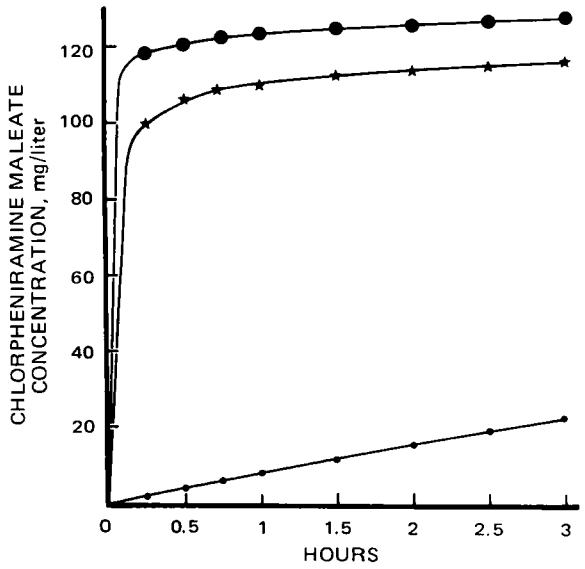

Figure 8—*Dissolution and dialysis profiles of a 1:5 chlorpheniramine maleate–montmorillonite sample, prepared from different grades of montmorillonite and run in 0.1 N HCl at 25°. Key: ●, dissolution, neutral montmorillonite; ★, dissolution, regular montmorillonite; and •, dialysis, neutral montmorillonite and regular montmorillonite.*

position of the equilibrium between drug adsorbed and free drug in solution (Scheme I). The pH of the medium may also affect this equilibrium.

$$\underset{\text{(free drug)}}{\text{drug} + \text{clay}} \rightleftharpoons \underset{\text{(complex drug)}}{\text{drug–clay}}$$

Scheme I

Anionic Drugs–Montmorillonite—In contrast to cationic-type drugs, which produced a thick curdy precipitate when added to the montmorillonite suspension, the addition of anionic drugs (*e.g.*, sodium salts of organic medicinals) simply caused a slight increase in viscosity. This effect was similar to that seen when an electrolyte such as sodium chloride was added to a suspension of montmorillonite.

This increase in viscosity was also evidenced when the nonionized drug sulfanilamide was added to the montmorillonite magma. This drug forms the anionic salt due to the many metal cations free in solution and the slightly alkaline pH of the suspension.

Since dissolution studies with these drug–montmorillonite adsorbates in an acid medium indicated that over 90% of drug was released after 30 min, fewer bioavailability problems would be anticipated with these systems.

Amphoteric Drugs–Montmorillonite—Both the nonionic xanthines theophylline and caffeine were found to bind moderately to montmorillonite. All samples contained 200 mg of the active ingredient with varying amounts of the clay. The dissolution and dialysis profiles for theophylline (Fig. 7) show approximately 50% of release from the 1:5 complex as compared to pure drug. The 1:5 complex of caffeine and montmorillonite released 42% of the drug into the dissolution medium. The appearance of the montmorillonite suspension after the addition of either xanthine indicated an increase in viscosity, as displayed by anionic drugs, plus a small degree of clumping, as exhibited by cationic drugs. This finding suggests that mechanisms other than physical adsorption were taking place.

The release profiles appear to confirm this deduction. Binding of theophylline appeared to be approximately of the same magnitude as amphetamine sulfate, although the amphetamine was more available from the complex in the acid medium. Caffeine (1,3,7-trimethylxanthine) and theophylline (1,3-dimethylxanthine) differ by the additional methyl group present on the caffeine molecule, so this functional group could account for 8% more caffeine than theophylline being bound by the same quantity of montmorillonite.

Introductory Mechanistic Studies—Bornstein (15) thoroughly reviewed the various types of bonding involved in drug–excipient interactions. The two limiting types of adsorption, physical and chemisorption, were discussed extensively by Monkhouse and Lach (16). Generally, the type of adsorption in most systems is not clear, although the extremes are easily distinguishable. It would be advantageous to characterize the nature of the surface of excipients if one were to examine the type of drug–excipient interaction closely. Unfortunately, the exact nature of very few surfaces is well understood.

Studies with anionic drugs and nonionics that form anionic moieties in the montmorillonite suspension showed that these drugs were bound weakly and were readily released from the drug–montmorillonite adsorbate. This reversibility of binding, leading to high concentrations of drug in the acid medium, was indicative of physical adsorption where weak van der Waals bonds were probably involved.

Additional experiments with respect to other effects were conducted utilizing drugs that were strongly bound to montmorillonite. Chlorpheniramine maleate and propoxyphene hydrochloride were the cationic drugs of choice.

The addition of a surfactant, polysorbate 80[8], to the acid medium prior to the 1:5 chlorpheniramine maleate–montmorillonite sample had little effect. The 4% increase in drug concentration in the medium after 3 hr indicated that forces stronger than physical adsorption were involved.

To investigate whether the pH of the clay was a key factor in the binding of cationic drugs, samples were prepared with chlorpheniramine maleate using both neutral (pH 7–7.5) and regular grade montmorillonite (pH 8.5–9). Release profiles of samples prepared from different grades of montmorillonite appear in Fig. 8. Dissolution studies showed that an additional 4% of the total drug was released from the neutral montmorillonite compared to the regular clay. This small difference may be explained by comparing the hydration of the two clays. The specially treated neutral montmorillonite does not hydrate nearly as well as the regular grade. This condition could result in less sites being exposed and available for drug adsorption, accounting for the difference seen in the dissolution profiles.

The lower content of sodium and potassium ions in the neutral clay may also be a factor. The dialysis profiles are the same for both grades of clay. The possibility exists for the formation of a quaternary nitrogen group in the drug molecule during the equilibration process. Quaternaries pass lipid or cellophane membranes at a much slower rate than does an uncharged drug moiety. This fact could account for a reduction in the dialysis rate of the drug from the neutral montmorillonite sample sufficient to render the dialysis profile identical with that found from the regular clay.

The effect of the equilibrating solvent on the binding of drugs to montmorillonite also was investigated using solvents of varying

[8] Tween 80.

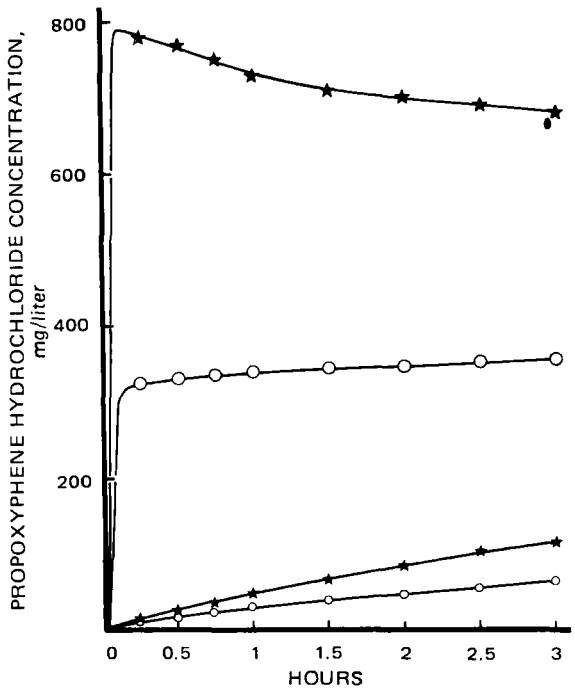

Figure 9—*Dissolution and dialysis profiles of a 1:2 propoxyphene hydrochloride–montmorillonite sample in 0.1 N HCl at 25°. Key: ★, dissolution, propoxyphene base equilibrated in methanol; ○, dissolution, propoxyphene hydrochloride equilibrated in water; ✶, dialysis, propoxyphene base equilibrated in methanol; and ○, dialysis, propoxyphene hydrochloride equilibrated in water.*

polarities. Carstensen and Su (11) showed that organic solutes free of cation-exchangeable groups adsorbed on the surface of neutralized montmorillonite and did not penetrate to the interior of the crystal. They showed that the nonionic drugs benzoic acid and diazepam (17), when equilibrated in nonaqueous solvents, were bound to neutral montmorillonite *via* an ion–dipole interaction. Since a surface physical adsorption was the proposed mechanism of binding, these authors stated that the montmorillonite adsorbates were bioavailable. Since their adsorption studies were carried out under nonaqueous conditions, it would be difficult to predict the bioavailability of drugs from the montmorillonite adsorbates without additional data.

When propoxyphene, which contains no cation-exchangeable groups, was added to a methanolic suspension of regular montmorillonite, no interaction was visible. Figure 9 shows the dissolution and dialysis profiles for propoxyphene base equilibrated in methanol and the drug hydrochloride salt equilibrated in water. Both samples were prepared as the 1:2 drug–montmorillonite complex and contained the same quantity of propoxyphene.

The dissolution curves in this figure are interesting; *e.g.*, over twice the quantity of drug was immediately released in solution from the methanol-equilibrated sample compared to the sample equilibrated in water. In this system, some of the base probably was bound *via* an ion–dipole type of surface adsorption, as suggested by Carstensen and Su (18). However, since only 60% of the drug was in solution after 15 min, this does suggest that forces stronger than those present in ion–dipole binding were responsible for the remaining 40% of the drug being strongly bound to the clay.

The "salting-out" phenomenon, evidenced by a decrease in the concentration of free drug in solution, could be due to the readsorption of drug back onto the clay. Propoxyphene in an acid medium is readily soluble since it forms the hydrochloride salt. In this ionized form, it can occupy sites on the montmorillonite where the base would not bind. Thus, in an acid medium the binding of the base to the montmorillonite would occur *via* the same mechanism as the hydrochloride salt under aqueous conditions.

However, when a cationic salt was equilibrated with regular montmorillonite using solvents of varying polarities (Table I), the binding and release profiles of the drug in the acid medium were very similar (Fig. 10). Consequently, it appears that if a drug is present as its cationic moiety, it would bind strongly to montmorillonite irrespective of the equilibrating solvent.

Table I—Influence of the Dielectric Constants of Equilibrating Solvent on Release of Chlorpheniramine from a 1:5 Drug–Montmorillonite Complex in 0.1 *N* HCl at 25°

Solvent	Dielectric Constant[a]	Chlorpheniramine in Solution, % After 15 min	Chlorpheniramine in Solution, % After 60 min
Water	78.5	19.8	23.3
Methyl alcohol	31.5	19.2	22.8
Acetone	19.1	19.9	22.3
Isopropyl alcohol	18.0	23.3	23.6

[a] Dielectric constants at 25°; from Ref. 23.

Wai and Banker (9), using radioactive sodium, confirmed the original claim by Grim (19) concerning the presence of exchangeable cations in montmorillonite clays. From their studies conducted in aqueous medium, Wai and Banker found that sodium in montmorillonite existed as the exchangeable cation as well as the free electrolyte. They concluded from their sorption profiles that, in an alcohol medium, the hydrochloride salts of the alkaloidal drugs studied were bound to the montmorillonite *via* cation exchange, surface adsorption, or a combination of both mechanisms or that they did not bind at all.

Studies in these laboratories suggested that cation exchange was one possible mechanism responsible for these interactions, although others also should be considered. The linear Langmuir adsorption isotherms found by Carstensen and Su (11, 18) in nonaqueous media and also obtained in this investigation (Fig. 6) in aqueous media seemed to indicate that surface adsorption was occurring rather than intercalation. It was also found that cationic drugs bind much stronger than anionic drugs. Since the surface of the montmorillonite carries a strong negative charge, it is possible that the drug was bound *via* a chemisorption interaction between the negative charge of the clay and the positive charge of the cationic moiety.

Figure 11 displays the influence of magnesium and sodium ions added to the montmorillonite suspension before and after the solution of chlorpheniramine maleate. Sodium chloride had a greater influence when added to the preformed complex than when it was added to the suspension before the drug. The opposite was true for magnesium chloride. When electrolytes were added to the clay suspension, an increase in viscosity was visible. This effect was not evident when the salts were added to the drug–clay suspension; the suspension had already lost the elegant stable appearance of the montmorillonite magma.

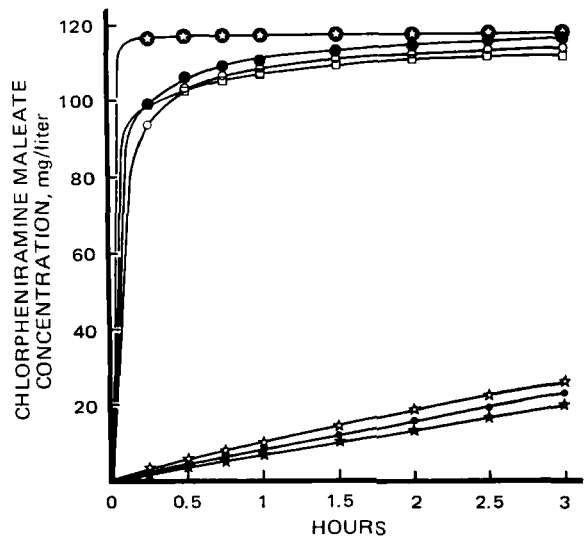

Figure 10—*Effect of preparing the sample in different solvents on the dissolution and dialysis profiles of a 1:5 chlorpheniramine maleate–montmorillonite sample in 0.1 N HCl at 25°. Key: ◎, dissolution, isopropyl alcohol; ●, dissolution, water; □, dissolution, acetone; ○, dissolution, methyl alcohol; ☆, dialysis, isopropyl alcohol; •, dialysis, water and methyl alcohol; and ★, dialysis, acetone.*

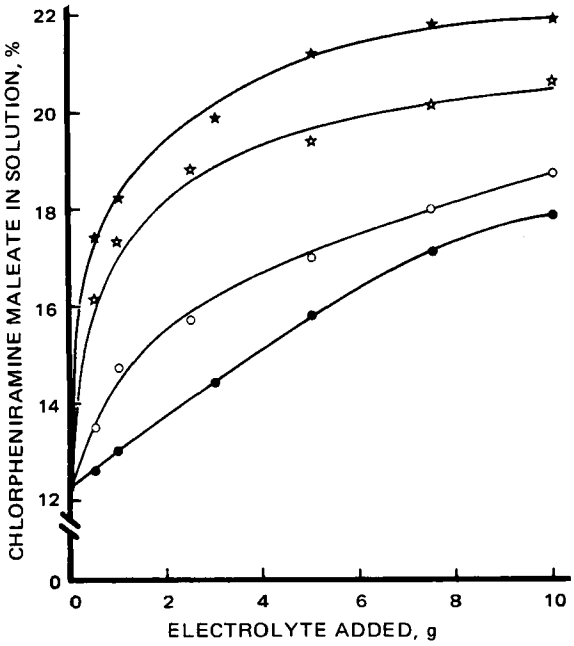

Figure 11—*Effect of electrolytes added to the montmorillonite suspension before (closed symbols) and after (open symbols) chlorpheniramine maleate. Key: ☆, ★, magnesium chloride (anhydrous); and ○, ●, sodium chloride.*

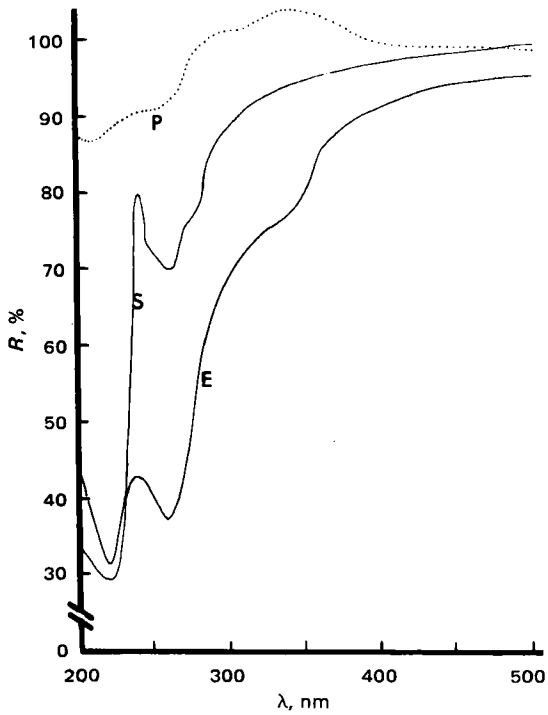

Figure 12—*Diffuse reflectance spectroscopy and UV spectra for chlorpheniramine maleate. Key: P, physical mix (diffuse reflectance spectroscopy); E, equilibrated (diffuse reflectance spectroscopy); and S, solution (UV, % T versus λ). Scale: % R = % T.*

When magnesium chloride solution was added to the montmorillonite suspension, it seemed logical that magnesium ions, being divalent, would be adsorbed to the clay surface more strongly than the singly charged sodium ions. This result would help explain why the divalent ions produced a higher concentration of free drug in solution than the monovalent ions. As the concentration of electrolyte was increased, the equilibrium would be in favor of exchange, making readsorption of drug onto the clay unlikely.

Although 10 g of sodium chloride added to the complex produced only a 7% increase in free drug in solution, this increase represented close to a 50% increase in the free drug concentration prior to the addition of the electrolyte. The degree of binding and amount of drug released were concentration dependent; *e.g.*, less free drug was found in solution if the volume was adjusted to 250 ml instead of 500 ml, all other parameters being constant.

The technique of diffuse reflectance spectroscopy was proposed by Lach and Bornstein (20–22) as a useful tool for the investigation of solid–solid interactions in pharmaceutical dosage forms. Diffuse reflectance spectroscopy was employed in the montmorillonite systems to study the surface interaction of drugs with the clay.

The diffuse reflectance spectrographs of percent reflectance *versus* wavelength for the physical and equilibrated sample appear in Fig. 12. Both samples contained the same quantity of drug. The lower reflectance (or higher absorbance) of the equilibrated sample signifies that the drug is surface coated onto the clay particles. The separation of peaks is not seen with the physical mix. The Kubelka–Munk theory predicts that the amount of radiant energy adsorbed will be directly proportional to the concentration of the adsorbing species present on the surface. Since little surface coating would be expected for the physical mix, most of the light beams are reflected.

At 340 nm, a shoulder appears in the equilibrated sample. The physical mix displays a peak at this wavelength, with reflectance being slightly greater than 100%. This finding cannot be fully explained at this time.

The S profile represents an aqueous solution spectrum of the drug (percent transmittance *versus* λ). The valleys for S occur at 223 and 262 nm. The valleys for reflective curve E for the equilibrated sample represent peaks of absorption and occur at 222 and 263 nm. This result indicates that the chromophores responsible for absorption at these wavelengths are not chemisorbed to the montmorillonite. The presence of a shoulder at 250 nm in profile S, not visible in profile E, and the shoulder at 271 nm in profile S, which is bathochromically shifted to 348 nm in profile E, are all indications of chemisorption.

SUMMARY AND CONCLUSIONS

The dissolution and dialysis results of this investigation indicated that cationic drugs and certain nonionic drugs bind tenaciously to montmorillonite clay. Anionic drugs and nonionics which exist as anionics, following their addition to the montmorillonite suspension, bind very weakly to the clay and pass rapidly into solution. The quantity of drug bound to the clay varied considerably from drug to drug.

For cationic drugs, it was proposed that the initial step in the binding mechanism was cation exchange. The cationic drug moiety exchanged with the bound metallic cation of the montmorillonite and then was bound to the clay *via* a strong chemisorption interaction between the positive charge of the drug and the negative charge on the clay surface. Reasons to support this two-step mechanism are as follows:

1. The quantity of chemisorbed drug was dependent on ionic concentration. As the salt content was increased, the binding of the drug decreased and less exchange took place. If electrolytes were added to the preformed drug–montmorillonite adsorbate in suspension, then the concentration of free drug in solution again increased. Readsorption of drug did not occur since the vacant sites on the clay were immediately reoccupied by the cations of the electrolyte.
2. Cationic drugs are readily soluble in hydrochloric acid, but very little drug was released from the adsorbate in this medium. This irreversible binding of the drug to montmorillonite was indicative of chemisorption.

The binding of the cationic salts to regular montmorillonite was very similar to that for the neutral grade of the clay. Consequently, the effect of the pH of the montmorillonite suspension appeared to be minimal on this drug–excipient interaction.

Diffuse reflectance spectroscopy studies suggested that specific functional groups in the drug molecule interact with the montmorillonite.

Finally, if one was not cognizant of interactions of montmorillonite with cationic drugs, then aqueous or nonaqueous solvents used in a wet granulation procedure would precipitate an interaction between the drug and clay excipient to decrease initial blood levels of the active substance. This problem would be particularly serious for drugs with low dosage, such as the antihistamines where immediate therapeutic levels of drug are required.

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NOTES

α- and β-Halomorphides: Stereochemistry, Analgesic Potency, Toxicity, and Interaction with Narcotic Receptors *In Vitro*

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Abstract □ The configuration of the halogen on the C-ring of several α- and β-halomorphides was determined by NMR. The analgesic potencies of these halomorphides and their interactions with narcotic receptors in rat brain homogenate were measured, as was the toxicity of the α- and β-chloromorphides. The halomorphides were examined as possible irreversible binders to the narcotic receptor.

Keyphrases □ Halomorphides, α and β—NMR determination of configuration of halogen on C-ring, analgesic potencies, toxicity, interaction with narcotic receptors studied □ Stereochemistry—α- and β-halomorphides, NMR determination of configuration of halogen on C-ring □ NMR—determination of configuration of halogen on C-ring of α- and β-halomorphides □ Analgesic agents—potency of α- and β-halomorphides compared □ Toxicity—α- and β-halomorphides compared

Recently, β-chloromorphide was found as a constituent of a clandestine opiate sample and was identified by comparison with a known sample (physical properties and mass and IR spectra) (1). Apparently the toxicity of this compound is unknown and the configuration of the halogen is uncertain, although its preparation, physical properties, and some biological data were described (2, 3).

α-Chloromorphide was isolated in this laboratory from a reaction between morphine and dimethylchloroformiminium chloride. Samples[1] of the known α- and β-chloromorphides, as well as the β-bromo- and β-iodomorphides, were obtained, and their biological activities and NMR spectra were determined. (From the NMR spectra, the configuration of the halide about the C-6 and C-8 positions in the C-ring could be deduced.)

IR spectral data were used to differentiate α-substituted codides (substituted on the C-6 position of the C-ring of the codide) from the β-substituted compounds (C-8-substituted compounds) (4). A relatively strong band at 940 cm^{-1} characterized the α-compounds, in agreement with a previous report (4). The β-compounds possessed a 900-cm^{-1} band and a 935–940-cm^{-1} band (medium to weak). NMR was used to differentiate clearly the α- and β-halomorphides and to obtain the orientation of halogen on the C-ring.

[1] Samples were obtained from Dr. E. L. May, National Institutes of Health.